also associated with fewer major bleeding events than aspirin. One can conclude that cilostazol is the preferred agent for secondary prevention of vascular events after stroke of arterial origin in Asian patients who do not have overt cardiac disease.

Effect of Fibroblast Growth Factor NV1FGF on Amputation and Death: A Randomized Placebo-Controlled Trial of Gene Therapy in Critical Limb Ischemia

Belch J, Hiatt WR, Baumgartner I, and the Tamaris Investigators. Lancet 2011;377:1929-37.

Conclusion: Nonviral 1 fibroblast growth factor (NV1FGF) does not reduce amputation or death in patients with critical limb ischemia.

Summary: Fibroblast growth factor type 1 (FGF1) activates migration, proliferation, and differentiation of endothelial cells. The result is sprouting of capillaries in pre-existing vessels. The gene encoding for human FGF1, when given intramuscularly in the calf or thigh via a naked DNA plasmid, leads to expression of human FGF1 protein. In an open-label phase 1 trial, a single intramuscular administration of NV1FGF in patients with critical limb ischemia improved pain, ulcer size, and hemodynamic variables (Comerota AJ, et al, J Vasc Surg 2002;35:930-6). The Therapeutic Angiogenesis Leg Ischemia Study for the Management of Arteriopathy and Non-Healing Ulcer (TALISMAN) results demonstrated a reduction of 63% in risk of major amputation and a 56% reduction of the risk of major amputation or death at 12 months compared with placebo, with no difference in the primary end point of ulcer healing (Nikol S, Mol Ther 2008;16:672-78). These two trials provided the stimulus for the phase 3 trial reported here. All patients had nonhealing ischemic skin lesions and were judged to be such that revascularization was not possible. There were 525 patients with critical limb ischemia unsuitable for revascularization. Patients were enrolled from 171 sites in 30 countries. All patients had minor skin gangrene or ischemic ulcers and met hemodynamic criteria for inclusion. Criteria included ankle pressure <70 mm Hg, or a toe pressure <50 mm Hg, or both, or a transcutaneous oxygen pressure <30 mm Hg on the treated leg. Patients were randomized in a 1:1 ratio to receive NV1FGF at 0.2 mg/mL or matching placebo. Patients and investigators were blinded to treatment. Each patient received eight intramuscular injections of their assigned treatment in their index leg on days 1, 15, 29, and 43. Primary end point was time to major amputation or death at 1 year. Data were analyzed on an intention to treat basis. There were 266 patients randomized to placebo and 259 to treatment with NV1FGF. All randomized patients were analyzed. Patients were a mean age of 70 years (range, 50-92 years), 70% were men, 47% had a history of coronary artery disease, and 53% had diabetes. The primary end point or components of the primary end point did not differ between treatment groups. Major amputation or death occurred in 86 patients in the placebo group and in 96 patients in the treatment group (HR, 1.11; 95% CI, 0.83-1.49; $P = .48$). No safety issues were identified with the use of NV1FGF in the treatment of critical limb ischemia.

Comment: A meta-analysis of trials that included gene-based and cell-based therapies in peripheral arterial disease concluded such therapies had potential clinical benefit (De Haro J, et al, Heart Vessels 2009;24:321-8). However, clinical benefit has not been demonstrated in rigorously controlled phase 3 trials. One can question the concept of the administration of a single gene where optimal dosage, routes of administration, duration of administration, and vectors of administration are all unknown. As currently performed, gene therapy trials are, unfortunately, still somewhat akin to "shots in the dark." One hopes the industry will not abandon the concept of gene therapy for vascular disease but will seek better preliminary data to optimize dosage, routes of administration, and vectors of administration of the genetic material.

How do the Type and Location of a Vascular Malformation Influence Growth in Klippel-Trenaunay Syndrome?

Funayama E, Sasaki S, Oyama A, et al. Plast Reconstruc Surg 2011;127: 340-6.

Conclusion: In Klippel-Trenaunay (KT) syndrome, abnormal subcutaneous tissue muscle and bone growth is associated with specific types and locations of vascular malformations.

Summary: KT syndrome is a mixed vascular malformation with a combination of capillary nevus, early onset varicosities, and hypertrophy of tissues and bones of the affected limb. KT has a wide variety of manifestations. Oduber et al in 2008, proposed a restrictive diagnostic criteria for KT syndrome (Ann Plast Surg 2008;60:217-223); group A: venous and capillary malformations; group B: abnormal growth of the effected limb. The authors retrospectively examined 35 patients who satisfied the diagnosis of KT syndrome by the criteria of Oduber et al. They examined the frequency of each type of vascular malformation and assessed relationships between vascular malformations (location and type) and abnormal limb growth (girth or length). Type and location of vascular malformation and abnormal circumferential growth were assessed by magnetic resonance imaging (MRI) and ultrasound imaging. Bone girth was assessed by axial MRI or computed tomography. Bone length was measured with plain radiographs of the long bones. The authors found no association between vascular malformation type with location or leg length. Leg bone circumferential hyperplasia was observed in 50% of cases and was related to the presence of intramuscular components of the malformation. A venous malformation in the subcutaneous tissue was significantly associated with the presence of subcutaneous hypertrophy. There was a higher frequency of muscle hyperplasia in patients with intramuscular lymphatic malformations.

Comment: One difficulty studying vascular malformations is achieving agreement on categorization and description. The criteria of Oduber et al are useful because they provide a precise description of the patients in the study. The observations that certain patterns of malformation influence patterns of subcutaneous or muscle hypertrophy may provide a starting point for determining what elements of a vascular malformation should be treated to maximize patient function in the long-term by normalizing muscle mass or decreasing subcutaneous hypertrophy.

Infectious Complications Following Conversion to Buttonhole Cannulation of Native Arteriovenous Fistulas: A Quality Improvement Report

Labriola L, Crott R, Desmet C, et al. Am J Kidney Dis 2011;57:442-8.

Conclusion: Infections events can be decreased with a buttonhole procedure of arterial venous access through intensive staff education.

Summary: Buttonhole cannulation of native arteriovenous fistulas (AVFs) with blunt needles was reported in 1977 (Twardowski Z, Contemp Dial Nephrol 1977;18:18-9). The technique has gained in popularity. In the buttonhole technique, the AVF is repeatedly accessed with blunt needles at the same site. A tunnel can be created from the skin to the AVF using a constant site over six hemodialysis sessions. The tunnel guides the blunt needle to the access vessel. Proponents argue the technique makes for easier cannulation, fewer missed sticks, less pain, and faster hemostasis after needle removal, with fewer hematomas and aneurysms. Because the buttonhole technique requires cannulation through nonhealed skin, it may lead to an increased risk of infectious events associated with AVFs. The authors conducted an observational study to determine whether infections events increased in patients with AVFs switched to buttonhole cannulation. They ascertained infectious events during four periods in their patients with AVFs. In period 1, the rope-ladder technique for access was used in all patients. Period 2 was characterized by a switch to the buttonhole technique. Period 3 was characterized by use of the buttonhole technique before there were educational workshops to minimize infectious complications. Period 4 included the interval after educational workshops on minimizing infectious complications. They analyzed 177 patients (mean age, 70.4 ± 11.5 years) with 193 AVFs. There were 186,481 AVF days available for analysis. During this time, 57 infectious events occurred (0.31 events/1000 AVF days). Infectious events incidents increased after switching to the buttonhole method (0.17 [95% CI, 0.086-0.31], 0.11 [95% CI, 0.0014-0.63], and 0.43 [95% CI, 0.29-0.61] event/1000 AVF days in periods 1, 2 and 3, respectively, $P = .003$). In period 4, infectious events incidents decreased to 0.34 events/1000 AVF days. Complicated infectious events (n = 12) were essentially restricted to period 3 (n = 11; 0.153 [95% CI, 0.076-0.273] events/1000 AVF days) with a significant decrease in period 4 (n = 1; 0.024 [95% CI, 0.001-0.118] events/1000 AVF days. The relative risk of a major infection in period 3 vs 4 was 6.37 (95% CI, 1.09-138.4, $P = .04$.)

Comment: Infections of native AVFs are infrequent, but this report did document an increase in infections and complications associated with the switch to buttonhole cannulations. The authors suspect that technicians accessing the fistulas became complacent with the hygiene protocol of the buttonhole technique. Their suspicion is somewhat supported by a subsequent decrease in infectious complications after institution of an educational program emphasizing proper hygiene in accessing of the AVFs with the buttonhole technique. The data are consistent with the recent emphasis of meticulous hygiene with access of any type of indwelling intravenous catheter or permanent vascular access device.

Neurosonographic Monitoring of 105 Spontaneous Cervical Artery Dissections

Baracchini C, Tonell S, Meneghetti G, et al. Neurology 2010;75:1864-70.

Conclusions: Changes in the lumen of cervical arteries afflicted with spontaneous cervical artery dissection occur most frequently within the first few months after the dissection, but recanalization may occur up to 1 year later. Early recurrence is reasonably common but involves arteries previously unaffected by dissection. Recurrence of spontaneous cervical artery dissection is strongly associated with a family history of arterial dissection.

Summary: It is generally acknowledged spontaneous cervical artery dissection (sCAD) is a highly dynamic process after the initial event. Information on recanalization and recurrence rates in patients with sCAD is limited, however. Although cervical artery mural hematomas are best detected by cervical magnetic resonance imaging (MRI) with T1 fat suppression, vascular ultrasound imaging is the test that is most frequently used to monitor patients with sCAD. In this study, the authors prospectively mon-